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HOFFMANN - EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München
ALLEMAGNE

Datum/Date: 04-01-2005

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
90731 a/fi	00962908.0-2117/1225174

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Sumitomo Chemical Company, Limited

COMMUNICATION OF A NOTICE OF OPPOSITION

Enclosed herewith is a copy of a notice of opposition to the European patent specified above.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (Rule 57(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (Rule 56 EPC).

Williams, Margit
Formalities Officer
Tel. No.: (089) 2399- 7272

Enclosure: Notice of opposition

OIV Dr. Dominique J. M. Trösch

BREUER & MÜLLER
PARTNERSCHAFT
PATENTANWÄLTE · EUROPEAN PATENT & TRADEMARK ATTORNEYS

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DR. MARKUS BREUER, DIPL.-CHEM.
MÜNCHEN

DR. BERNHARD MÜLLER, DIPL.-CHEM.
SEEFELD

PARTNERSCHAFT
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PLEASE REPLY TO:

DR. MARKUS BREUER
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17 December 2004

Application/Patent: **00962908.0/EP 1 225 174**
Title: **Anhydrous Mirtazapine Crystals and Process for the Production thereof**
Applicant/Proprietor: **Sumitomo Chemical Company, Ltd., 27-1, Shinkawa 2-chome, Chuo-ku Tokyo 104-8260/JP**

My Reference: **M1-1-B-EP1**
Keyword: **Mirtazapine Hydrate**

Zur Kasse

In the name and on behalf of

Dr. Dominique J. M. Trösch,
Ermlandstraße 12,
D-81929 Munich

an Opposition against the grant of the above-identified patent is herewith filed.

Please debit the opposition fee from deposit account 2800 1035.

1. Requests

It is requested to revoke the patent EP-B-1 225 174 (hereinafter referred to as "Opposed Patent") in its entirety. Oral proceedings are requested by way of an auxiliary request in accordance with Art. 116 EPC.

2. Grounds for Opposition

The opposition is filed on the ground that the subject-matter of the European Opposed Patent is not patentable within the terms of Articles 52 to 57 EPC (Article 100(a) EPC). In particular, the subject-matter of the Opposed Patent lacks novelty (Article 54 EPC) and inventive step (Article 56 EPC). Furthermore, a lack of sufficient disclosure is also objected (Article 100(b) EPC).

3. Documents Cited

The following documents are cited in the opposition:

D1 WO 00/62782 A1

D2 F.M. Kaspersen et al., Journal of Labelled Compounds and Radio-pharmaceuticals (1989), 27(9), 1055-68

D3 Experimental Report

D4 US 4 062 848

D5 Approval Letter for Remeron™ (Mirtazapine), Center for Drug Evaluation and Research, US Food and Drug Administration, 14 June 1996

D6 "Environmental Impact Assessment Report for Remeron™", 30 October 1995, Pages 1, 2 and 11

D7 DSC Results of Mirtazapine Products

4. Subject-Matter of the Independent Claims of the Opposed Patent

Claim 1 of the Opposed Patent is directed to low-hygroscopic anhydrous Mirtazapine crystals having a hygroscopicity of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours.

It is submitted that the terms "low-hygroscopic" and "anhydrous" are vague and cannot serve as distinguishing features over prior art.

Claim 3 relates to a process for preparing mirtazapine crystals according to claim 1 by drying crystals of Mirtazapine hydrate.

Claim 7 of the Opposed Patent is directed to a Mirtazapine hydrate containing 1/n molecules of H_2O per molecule of Mirtazapine, wherein n is an integer of 1 to 5. This can be alternatively expressed by the percentage of water content of the Mirtazapine hydrate.

For the conversion between molar amount and percentage, the molecular weight of Mirtazapine has to be taken into consideration ($C_{17}H_{19}N_3$, M.W. = 265.36). For n = 1, the percentage water content amounts to 6.36% (18.02/(18.02 + 265.36) x 100). For n = 5, the water content is 1.34% ((18.02/5)/(18.02/5 + 265.36) x 100). In other words, claim 7 covers crystalline hydrates of Mirtazapine having a water content between 1.34% and 6.36%.

The percent water content values for the individual hydrates are listed in the table below.

n	Water Content (wt %)
1	6.36
2	3.28
3	2.21
4	1.67
5	1.34

Claim 8 relates to a process for preparing Mirtazapine hydrate by crystallizing crude Mirtazapine using a water soluble organic solvent and water.

5. Priority

The Opposed Patent claims priorities of JP 33304999 (24 November 1999), JP 2000067476 (10 March 2000) and WO/PCT/JP00/04835 (19 July 2000).

The proprietor admitted during the examination procedure, that the effective date of claims 1 and 2 is 10 March 2000 (see letter dated 8 May 2003). Furthermore, it is submitted that 10 March 2000 is the effective date for claims 3 and 5, since subject-matter of those claims was first disclosed in JP 2000067476.

Claims 4, 6 and 7 seem to have an effective date of 19 July 1999.

However, the subject-matter of claims 8 to 11 cannot be found in anyone of the claimed priority documents. Therefore, it is submitted that the filing date 28 September 2000 is the effective date for claims 8 to 11.

6. Lack of Novelty

6.1 Relevant Prior Art

WO 00/62782 A1 (D1) was filed on 18 April 2000. It claims a priority of 19 April 1999 (US 19990130047P) and a priority of 16 February 2000 (US 20000182745P). Document D1 designates the same contracting states as the Opposed Patent and all steps necessary to enter the regional phase before the EPO have been conducted in due time. As far as the disclosure of US 20000182745P is concerned, D1 is prior art with respect to claims 1, 2, 3, 5 and 8 to 11 of the Opposed Patent according to Art. 54 (3) in conjunction with Art. 158 (1) EPC.

Document D2 was published in 1989. US 4 062 848 (D4) was published on 13 December 1977. Therefore, those documents are prior art with respect to claims 1 to 11 of the Opposed Patent according to Art. 54 (2) EPC.

D5 documents the approval of a Mirtazapine product, Remeron™, by the US Food and Drug Administration (FDA) before the priority of the Opposed Patent.

D6 is an extract from the approval documents which are publicly available from the FDA under the Freedom of Information Act since the grant of the market authorization. Therefore, document D6 is prior art with respect to claims 1 to 11 of the Opposed Patent according to Art. 54 (2) EPC.

6.2 Lack of Novelty of Claims 1 and 2

6.2.1 Claim 1 is not Novel in View of D1

The subject-matter of claim 1 is not new in view of document D1.

Document D1 discloses on page 9, line 30 to page 10, line 17 and in example 6 pure Mirtazapine crystals. The disclosed embodiments have an effective date of 16 February 2000, since they are also disclosed in US 20000182745P.

The Mirtazapine crystals of example 6 of D1 are obtained by the same process as the Mirtazapine hemihydrate of example 6 of the Opposed Patent.

	Opposed Patent	D1
Educts	Crude Mirtazapine	Crude Mirtazapine
Solvent	methanol/water	methanol/water (see table1)
Drying conditions	60 °C	60 °C

Therefore, D1 discloses crystalline Mirtazapine hydrates (see also page 10, lines 21/22 of D1).

However, the crystalline Mirtazpine hydrates disclosed in D1 are novelty destroying for subject-matter of claim 1 since the term "anhydrous" is vague and cannot serve as a distinguishing feature over prior art.

Furthermore, the crystalline Mirtazapine hydrates disclosed in D1 are also novelty destroying for subject-matter of claim 2, since the feature "having a water content of not more than 0.5 %" is only a feature relating to the purity level of the claimed Mirtazapine, because the purity level of the Mirtazapine claimed in claim 2 is up to 99,5 % pure Mirtazapine, whereas the purity level of a Mirtazapine hydrate having a water content of 3 % as disclosed on page 10, lines 21/22 of D1 is up to 97 %.

However, the purity level of a known chemical compound, which is achieved by means of conventional purification methods can not establish novelty over the known compound. See T990/96:

"Conventional methods for the purification of low molecular organic reaction products such as recrystallisation [...] which normally can be successfully applied in purification steps are within the common general knowledge of those skilled in the art. It follows that, in general, a document disclosing a low molecular chemical compound and its manufacture makes available this compound to the public in the sense of Art. 54 EPC in all grades of purity as desired by a person skilled in the art."

Moreover it is submitted that the crystals disclosed in D1 inevitably have a hygroscopicity of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours. If the proprietor wants to establish novelty on the basis of this parameter, he has to submit clear and convincing evidence that the crystals disclosed in D1 do not fulfil this requirement.

6.2.2.1 Claims 1 and 2 are not Novel in View of D2

Document D2 discloses Mirtazapine hydrate (see arguments submitted under 6.4.1 of this brief of opposition).

However, the Mirtazapine hydrate disclosed in D2 destroys novelty of subject-matter of claims 1 and 2, in accordance with the arguments submitted under 6.2.1 of this brief of opposition.

6.2.3 Claims 1 and 2 are not Novel in View of D4

D4 discloses a process for the preparation of Mirtazapine wherein the crude reaction product is recrystallized from petroleum ether 40-60 (see col. 11, lines 10 to 26 of D4).

Since the Mirtazapine crystals obtained in example 1 of D4 have **exactly** the same melting point as the Mirtazapine crystals prepared in accordance with example 7 of the Opposed Patent, it is submitted, that the crystals of D4 and the crystals claimed in claims 1 and 2 are identical with regard to their chemical structure. Therefore, claims 1 and 2 are not novel over the Mirtazapine crystals disclosed in D4.

It is furthermore submitted, that comparative example 3 of the opposed patent is not suitable to compare the crystals of D4 with the crystals of Example 7 of the present invention, since comparative example 3 of the opposed patent has not been carried out under the same conditions as disclosed in D4.

6.2.4 Claims 1 and 2 are not Novel in View of D5 / D6

The drug REMERON™ comprising the ingredient "Mirtazapine" was approved by the FDA on 14 June 1996 (REMERON™ 15 mg and 30 mg tablets) (see D5).

On page 11 of D6 the ingredient is identified as crystalline Mirtazapine having a melting point of 120°C to 124°C.

The crystalline Mirtazapine disclosed in D6 destroys novelty of subject-matter of claims 1 and 2, in accordance with the arguments submitted under 6.2.1 of this brief of opposition.

6.3 Lack of Novelty of the Subject-Matter of Claims 3

Document D1 anticipates the subject-matter of claim 3 in example 6. Therefore, subject-matter of claim 3 lacks novelty over document D1.

6.4 Lack of Novelty of the Subject-Matter of Claim 7

6.4.1 Claim 7 is not Novel in View of D2

Document D2 by F.M. Kaspersen et al. in the Journal of Labelled Compounds and Radiopharmaceuticals (1989), 27 (9), 1055-68 entitled "The Synthesis of ORG 3770 Labelled with ^{3}H, ^{13}C and ^{14}C" identifies Mirtazapine, as follows from the chemical name and the structural formula given in the publication (code "Org 3770"). Regarding the purification of Mirtazapine, the following is disclosed:

> *"For final purification the product was treated twice with 100mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colourless crystals, m. p. 123,8-125,8°C. No impurities were detectable on TLC, HPLC or GC."* (see D2, page 1066, first paragraph)

As methanol is a water soluble organic solvent, the quoted passage describes crystallizing crude Mirtazapine using a water-soluble organic solvent and water. On behalf of the Opponent experiments have been carried out in order to measure the water content of the Mirtazapine crystals obtained by the process according to D2 (see Experimental Report D3).

In the Experimental Report (D3) the preparation of Mirtazapine has been carried out exactly as described in the above mentioned page of D2. The experiments show that the resulting crystals have a water content of 3.07 percent and a melting point from 119.7°C to 121°C.

To summarize, document D2 discloses Mirtazapine crystals having a water content, which inevitably leads to chemical compounds falling under the scope of claim 7 (see also point 4 of this brief of opposition). Therefore, subject-matter of claim 7 is not novel over document D2.

6.4.2 Claim 7 is not Novel in View of D4

D4 discloses a process for the preparation of Mirtazapine wherein the crude reaction product is recrystallized from petroleum ether 40-60 (see col. 11, lines 10 to 26 of D4). Since the crystals obtained in example 1 of D4 have exactly the same melting point as the Mirtazapine crystals prepared in accordance with example 7 of the Opposed Patent, it is submitted, that the crystals of D4 show a water content of less than 0.5 %.

However, the crystalline Mirtazapine disclosed in D4 is also novelty destroying for subject-matter of claim 7, since the feature "having a water content of at least 1.34 %" (which is the technical "translation" of formula (I) of claim 1, see above section 4 of this submission) is only a feature relating to the purity level of the claimed Mirtazapine, because the purity level of the Mirtazapine claimed in claim 7 is up to 98.64 % pure Mirtazapine, whereas the purity level of a Mirtazapine according to D4 might be even higher (since the water content is lower).

As discussed above (see section 6.2.1) the purity level of a known chemical compound, which is achieved by means of conventional purification methods can not establish novelty over the known compound; see T990/96. In the present case, the cited decision of the Board of Appeal does not apply directly. However, in reverse it is submitted that if novelty cannot be established by further purifying, i.e. increasing the level of purity of a known compound, novelty also cannot be established by decreasing the level of purity of a known compound.

As a result, the Mirtazapine crystals of D4 having a high purity are novelty destroying for the claimed Mirtazapine crystals of claim 7, having a lower purity.

6.4.3 Claim 7 is not Novel in View of D6

On page 11 of D6 the ingredient is identified as crystalline Mirtazapine having a melting point of 120°C to 124°C. According to the melting range of the crystals, D5 discloses a crystalline Mirtazapine in form of a hydrate.

The crystalline Mirtazapine disclosed in D6 destroys novelty of subject-matter of claim 7, in accordance with the arguments submitted under section 6.2.1 and 6.4.2. of this brief of opposition.

6.4.4 Claim 7 is not Novel in View of Prior Art Mirtazapine Products

As already mentioned, products containing Mirtazapine were already marketed before the priority date of the Opposed Patent. This is in particular true for Remeron™ as approved by the US Food and Drug Administration (see D5).

The Opponent does not leave a sample of this product at his disposal. However, on behalf of the Opponent, several Mirtazapine products as marketed by the innovator in Europe were investigated by DSC. The results are reported in D7. They show that these products contain Mirtazapine in the form of the hemihydrate. It would be entirely unreasonable to assume that Mirtazapine in Remeron™ has a different form. Thus, the subject-matter of claim 7 is anticipated by the prior art Remeron™ product.

6.5 Lack of Novelty of the Subject-Matter of Claims 8 to 11

D1 discloses a method for producing crystals of a Mirtazapine hydrate by suspending crude Mirtazapine in ethanol and adding water to the resulting solution, see page 13, lines 13 to 23 and example 6 of D1. Furthermore, in table 1 of D1 mixed solvents comprising water-soluble organic solvents and water are disclosed. Therefore, subject-matter of claims 8 and 9 lacks novelty over document D1.

D2 discloses the crystallization of Mirtazapine from a methanol/water mixture, see page 1066 of D2. Therefore, subject-matter of claims 8 and 9 lacks novelty over document D2.

D1 discloses in example 6 recrystallization of crude Mirtazapine by suspending the crude Mirtazapine in ethanol and subsequently adding water. Therefore, subject-matter of claim 10 lacks novelty over document D1.

In example 6 D1 discloses recrystallization of crude Mirtazapine by suspending the crude Mirtazapine in ethanol and subsequently adding water, wherein the temperature is cooled to 10°C. Therefore, subject-matter of claim 11 lacks novelty over document D1.

7. Lack of Inventive Step

7.1 Lack of Inventive Step of Claim 1, 2 and 7 in View of Documents D2, D4, D5 and D6

As shown above in section 6., the Opponent is of the opinion that the subject-matter of claims 1, 2 and 7 is not novel in view of documents D2, D4, D5 and D6.

It is submitted that even if certain features of the claimed subject-matter should not be considered by the Opposition Division to be identical in every detail with those of the cited prior art documents (D2, D4, D5 and D6 respectively), these differences would be in any case very minor and consequently not sufficient to impart an inventive step to the claimed subject matter. Therefore, Opponent reverses in accordance with T 0131/01 the right to substantiate the ground of lack of inventive step according to the problem-solution-approach in more detail, at least when the Opposition Division makes clear which feature of the claimed subject-matter has to be regarded as not disclosed by the cited prior art.

See headnote of T 0131/01:

> *"... a specific substantiation of the ground of lack of inventive step is neither necessary [...] nor generally possible without contradicting the reasoning presented in support of lack of novelty."*

7.2 Lack of Inventive Step of Claims 3 to 6

The subject-matter of claim 3 of the Opposed Patent is not inventive in view of D2 in combination with general knowledge of a skilled person.

Document D2 might be considered as closest prior art. D2 discloses the preparation of Mirtazapine crystals.

The only difference between the disclosure of D2 and the process claimed in claim 3 of the Opposed Patent is the drying step.

Due to the above distinguishing feature the Opposed Patent provides crystals having a lower water content. Therefore, the technical problem to be solved was to provide a process for the preparation of crystalline Mirtazapine having a lower water content than the Mirtazapine crystals known in D2.

The skilled person, who is a chemist at least skilled in laboratory work, when confronted with this problem would certainly have employed a drying step since every chemist knows that the water content of chemical compounds usually can be reduced by drying. The subject-matter of claim 3 can thus not be regarded as inventive in view of document D2.

The subject-matter of claim 4 of the Opposed Patent is not inventive in view of D2 in combination with general knowledge of a skilled person since it is trivial knowledge of a chemist to pulverize crystals before drying.

The subject-matter of claim 5 of the Opposed Patent is not inventive in view of D2 in combination with general knowledge of a skilled person.

It has been shown in section 6.4.1 that document D2 discloses a Mirtazapine hydrate falling under the general formula (I) of claim 5. Furthermore, the arguments above regarding lack of inventive step of claim 3 also apply to claim 5. It would have been obvious for a skilled person to dry the Mirtazapine hydrate of D2 if crystals having a lower water content would have been the object.

The subject-matter of claim 6 of the Opposed Patent is not inventive in view of D2 in combination with general knowledge of a skilled person since it is an ordinary skill for a chemist to perform drying by heating and reducing pressure.

7.3 Lack of Inventive Step of Claims 8 to 11

The subject-matter of claim 8 of the Opposed Patent is not inventive in view of D4 in combination with general knowledge of a skilled person.

Document D4 might be considered as closest prior art. D4 discloses the crystallization of crystalline Mirtazapine from crude Mirtazapine in petrol ether.

The only difference between the disclosure of D4 and the process claimed in claim 8 is the choice of the solvent.

Due to the above distinguishing feature the Opposed Patent provides crystals having a higher water content. Therefore, the technical problem to be solved was to provide a process for the preparation of crystal Mirtazapine having a higher water content than the Mirtazapine crystals known in D4.

The skilled person, who is a chemist at least skilled in laboratory work, when confronted with this problem would certainly have employed a water-soluble

organic solvent and water, since a chemist knows that the water content of chemical compounds usually can be increased by recrystallization in a water containing organic solvent (water alone is not possible since Mirtazapine is not soluble in water). The subject-matter of claim 8 can thus not be regarded as inventive in view of document D4.

The subject-matter of claims 9, 10 and 11 of the Opposed Patent is not inventive in view of D4 in combination with general knowledge of a skilled person since the features of said claims only describe ordinary skills of a chemist.

8. Lack of Sufficient Disclosure

Claim 1 of the Opposed Patent stipulates that the anhydrous Mirtazapine crystals have a hygroscopicity of not more than 0.6 % by weight when the crystals are stored in the air having a relative humidity of 75 % at 25°C under atmospheric pressure for 500 hours. The same feature is also contained in the independent process claim 3.

This feature is, however, merely a repetition of one of the problems underlying the alleged invention, namely the provision of anhydrous Mirtazapine crystals having low hygroscopic properties. Thus, unless anhydrous Mirtazapine crystals automatically show a hygroscopicity as required by claims 1 and 3, there is no sufficient disclosure. In this context, it is also pointed out that the specification only teaches the conventional drying of Mirtazapine to obtain the desired anhydrous crystals. Should conventional drying of Mirtazapine not lead to a product as defined in claims 1 and 3, then the patent is insufficient as there is no disclosure of any specific means which would allow the preparation of anhydrous crystals having specific properties not achieved by routine drying.

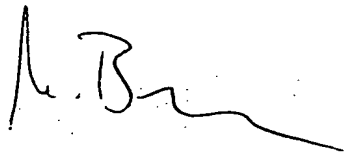
The same considerations apply with respect to the claims dependent on claim 1 or claim 3.

Claim 7 of the Opposed Patent is directed to a Mirtazapine hydrate containing 1/n molecules of water per molecule of Mirtazapine, wherein n is an integer of 1 to 5. It has been suggested above that this definition actually means that hydrous Mirtazapine crystals containing an amount of water of between 1.34 to 6.36 weight-% of water are claimed. Should the Proprietor take the view that claim 7 is actually directed to stoichiometric hydrates containing exactly 1, 1/2, 1/3, 1/4 or 1/5 molecules of water per molecule of Mirtazapine, then it is submitted that the patent does not disclose how such specific hydrates could be prepared.

A similar objection would apply to the process claims 8 to 11 should they be construed in such a way that they are directed to the preparation of specific stoichiometric hydrates.

9. Summary

As has been shown above, the subject-matter of claims 1 to 11 of the Opposed Patent does not meet the requirements of the Art. 54 and 56 EPC. Furthermore, the requirement of a sufficient disclosure is also not fulfilled. Therefore, the request to revoke the Opposed Patent in its entirety is fully justified.



Dr. Markus Breuer
European Patent Attorney

Enclosure: Documents D1 to D7

EP-B-1 225 174 (Appl.nr. 00962908.0)
Opponent: Dr. Dominique Trösch

Experimental Report (D3)

Mirtazapine crystals (Org 3770) according to pages 1065 and 1066 of D2 (F.M. Kaspersen et al., Journal of Labelled Compounds and Radiopharmaceuticals (1989), 27(9)) have been prepared.

Since D2 does not teach specific drying conditions, standard conditions of the art have been chosen. The resulting crystals have been dried for 4 hours and 40 minutes at 20 °C under vacuum. The parameters below have been measured.

Melting Point: 119.7 – 121.0°C
Water Content: 3.07 %

NDA 20-415

JUN 14 1996

Organon Inc.
Attention: Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Mayo:

Please refer to your New Drug Application (and your resubmission dated January 26, and received on January 30, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron™ (mirtazapine) 15 and 30 mg Tablets to treat depression.

We also refer to an Agency approvable letter dated January 26, 1996, and we also acknowledge receipt of your additional communications dated March 15, and May 10, 1996, providing for responses to our approvable letter.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated May 10, 1996. Accordingly, the application is approved effective as of the date of this letter.

Accompanying this letter (ATTACHMENT) is the labeling, including the revisions agreed to, that should be used for marketing this drug product. These revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

We have the following additional comments:

Phase 4 Commitments

We remind you of your Phase 4 commitments agreed upon in your submissions dated March 15, and May 10, 1996. These commitments are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

1. Exploration of Dose Response for Effectiveness/Exploration of Dose Response and Time Course for Sedative Effects of Mirtazapine

   We note your commitment in correspondence dated May 10, 1996, to conduct a fixed dose response/somnolence study that will explore dose response for both antidepressant effectiveness and for somnolence. We also note your commitment to initiate this study in early 1997 and to complete this study by mid 1998.

2. Long-Term Efficacy Studies

   We note your commitment in correspondence dated May 10, 1996, to conduct a relapse prevention study. We also note your commitment to initiate this study in early 1997 and to complete this study by early 1999.

3. Mouse Carcinogenicity Study

   We accept your plan to perform a pilot 2 week dietary study in mice. Depending on the results of this study, we acknowledge your commitment to conduct a 3 month dietary administration study in mice to obtain exposure data which will allow us to determine whether or not the mouse carcinogenicity study was adequate.

Biopharmaceutics

We note your agreement to the following dissolution method and specification for all tablet strengths:

Apparatus:
Paddle Speed:
Medium:
Specification:

Manufacturing and Controls

As acknowledged in your correspondence dated May 10, 1996, the Agency is approving an initial 24-month expiration dating period based upon your currently available 24 -month data.

Special Reporting Requirement for Selected Spontaneous Reports

In order to facilitate our efficient review and evaluation of data pertinent to hematologic and hepatic toxicity, we ask that you submit any spontaneous reports for adverse events of these types as 15 day reports.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions concerning this NDA, please contact Mr. Paul David, Project Manager, at (301) 594-2777.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

ATTACHMENT

REMERON™
(mirtazapine) Tablets

DESCRIPTION

REMERON™ (mirtazapine) is an antidepressant for oral administration. It has a tetracyclic chemical structure, unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:

[Insert structural formula here.]

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory

autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In-vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine

after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Clinical Trials Showing Effectiveness

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies

demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the

... drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC < 500/mm³ without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of Remeron treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of Remeron. Because of Remeron's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron.

Increased Appetite/Weight Gain

In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients in long-term, open label treatment, 8% of patients receiving Remeron discontinued for weight gain.

Cholesterol/Triglycerides

In U.S. controlled studies, nonfasting cholesterol increases to ≥ 20% above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to Remeron in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON™ (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON™ (mirtazapine) treated patients in U.S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

Clinical experience with REMERON™ (mirtazapine) in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with

diseases or conditions that affect metabolism or hemodynamic responses.

Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. REMERON™ should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may

tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that Remeron therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

As with other drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (See CLINICAL PHARMACOLOGY).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. In vitro studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON™ (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200

mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

REMERON™ was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, in vitro gene mutation assay in Chinese hamster V 79 cells, in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, in vivo bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, Remeron™ was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m² basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with Remeron™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights.

The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering Remeron to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

Approximately 16 percent of the 453 patients who received Remeron in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of the 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (Remeron incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Remeron-treated patients who participated in short-term U.S. placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

INCIDENCE OF ADVERSE CLINICAL EXPERIENCES[1] (≥1%) IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema.	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

1 Events reported by at least 1% of patients treated with Remeron (mirtazapine) are included, except the following events which had an incidence on placebo ≥ Remeron.

nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of Remeron who experienced an event of the type cited on at least one occasion while receiving Remeron. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with Remeron, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent

[illegible] those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: *frequent*: malaise, abdominal pain, abdominal syndrome acute; *infrequent*: chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare*: cellulitis, chest pain substernal.

Cardiovascular System: *frequent*: hypertension, vasodilatation; *infrequent*: angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare*: atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: *frequent*: vomiting, anorexia; *infrequent*: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; *rare*: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: *rare*: goiter, hypothyroidism.

Hemic and Lymphatic System: *rare*: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: *frequent*: thirst; *infrequent*: dehydration, weight loss; *rare*: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: *frequent*: myasthenia, arthralgia; *infrequent*: arthritis, tenosynovitis; *rare*: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: *frequent*: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; *infrequent*: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal

[illegible], coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; *rare:* aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: *frequent:* cough increased, sinusitis; *infrequent:* epistaxis, bronchitis, asthma, pneumonia; *rare:* asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: *frequent:* pruritus, rash; *infrequent:* acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare:* urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: *infrequent:* eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; *rare:* blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: *frequent:* urinary tract infection; *infrequent:* kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, *rare:* polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated

carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were eight reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of Remeron, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups compared to levels observed in younger adults without renal or hepatic impairment. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with Remeron. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC# 0052-0105-30
Bottles of 100	NDC# 0052-0105-91
Bottles of 500	NDC# 0052-0105-95
Unit Dose, Box of 100	NDC# 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30	NDC# 0052-0107-30
Bottles of 100	NDC# 0052-0107-91
Bottles of 500	NDC# 0052-0107-95
Unit Dose, Box of 100	NDC# 0052-0107-90

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68° - 77°F) [See USP]

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.

Doc LABMRTDP.AP1

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Remeron™

(mirtazapine)

Tablets 15mg/30mg

NDA 20-415

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Neuropharmacological Drug Products HFD-120

Project: REMERON™
Document No.: PDR-211.03

REDACTIONS MADE BY APPLICANT

ORGANON INC.
West Orange, New Jersey 07052

ENVIRONMENTAL IMPACT ASSESSMENT REPORT FOR REMERON™

REVISION 03

Pharmaceutical Development Department
Product Development and Government Affairs
October 30, 1995

1661

REDACTIONS MADE BY APPLICANT

ENVIRONMENTAL IMPACT ASSESSMENT REPORT FOR REMERON™ - REVISION 03

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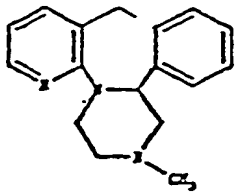
5. Identification of Chemical Substances that are Subject to the Proposed Action:

5.1 Drug Substance

5.1.1 Names:

United Stated Adopted Name (USAN):	Mirtazapine
CAS Registry Number:	85650-52-8
Laboratory Code Name:	ORG 3770
Trade Name:	Remeron™
Chemical Names:	(1) pyrazino [2,1-a]pyrido[2,3-c][2] benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-
	(2) 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c] benzazepine

5.1.2 Physical and Chemical Characteristics:

Molecular Formula	$C_{17}H_{19}N_3$
Molecular Mass	265.36
Structural Formula.	
Appearance:	White to creamy white crystalline powder
Melting Point:	120°C-124°C
Solubility:	n-Hexane: 10 mg/mL Toluene: 150 mg/mL Methanol: 350 mg/mL Diethylether: 35 mg/mL Water: Practically insoluble

EP-B-1 225 174 (Appl.nr. 00962908.0)
Opponent: Dr. Dominique Trösch

DSC Results of Mirtazapine Products (D7)

DSC (differential scanning calorimetry) experiments in open and in sealed pans have been performed. It has been found that:

- a hydrated product shows a different behaviour when using sealed pan as compared to using open pan
- an anhydrous product has the same behaviour when using sealed pan and when using open pan

More precisely, the hydrated product shows a peak for the DSC in a sealed pan at about 122-123°C while that for an open pan lies between 115-117°C. The anhydrous product shows a peak for the DSC in a sealed pan at about 115-117°C and in an open pan at about 115°C.

The lots of finished dosage form that have been analysed by DSC are:

Remeron 576161 (innovator's marketed finish dosage form in UK)
Remergil 4939401 (innovator's marketed finish dosage form in Germany)
Remeron 355904 (innovator's marketed finish dosage form in Austria)
Remeron 597837 (innovator's marketed finish dosage form in Portugal)
Zispin 537051 (innovator's marketed finish dosage form in Ireland)
Rexer 615719 (innovator's marketed finish dosage form in Spain)

As already mentioned, there is a significant difference (about 6-7°C) between the peaks in the DSC for the sealed and open pan in the case of hydrated material, whereas that difference tends to be negligible in the case of anhydrous material. From the observation of the DSC graphs of all finished dosage forms analysed by DSC, it has to be concluded that the product present in all of the finished dosage form analysed corresponds to Mirtazapine hemihydrate.